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Neurocognition in young offspring of individuals with bipolar disorder: The role of co-existing familial and clinical high-risk for bipolar disorder

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ABSTRACT

Bipolar disorder (BD) is associated with cognitive dysfunction which has also been reported in offspring of individuals with BD (BDoff). However, it remains unclear whether cognitive underperformance in BDoff is associated with the presence of history of subclinical syndromes associated with risk for BD. To address this knowledge gap we assessed executive function, visual and verbal memory, working memory, processing speed and verbal fluency in 21 offspring with clinical high risk (CHR; BDoff + CHR), 54 offspring without CHR (BDoff-non-CHR), and 50 healthy individuals without familial risk of BD. BDoff underperformed compared to controls in most cognitive tasks. There was no significant neurocognitive difference between BDoff + CHR and BDoff-non-CHR except in the fluency/central executive domain (Cohen's $d = 0.60$, $p = 0.03$). Our results suggest that cognitive dysfunction in multiple domains is associated with familial predisposition to BD regardless of CHR status. On the other hand, abnormalities in central executive processes might be more pronounced in BDoff + CHR than BDoff-non-CHR. Further longitudinal studies investigating cognitive trajectory of BDoff and its interaction with the emergence of subclinical syndromes are needed to fully characterize the relationship between cognition and mood dysregulation in BD.

1. Introduction

Bipolar disorder (BD) is associated with significant cognitive dysfunction that is present during episodes and persists in euthymia (Arts et al., 2008; Bora et al., 2009; Bora et al., 2016a; Man-Wrobel et al., 2011; Raucher-Chéné et al., 2017; Torres et al., 2007). Cognitive dysfunction in BD is evident in a wide range of domains including verbal memory, executive functions, verbal fluency, working memory, visual memory, attention, theory of mind and processing speed (Arts et al., 2008; Bora et al., 2009; Bora et al., 2016b). However, the timing of the emergence of cognitive dysfunction in BD is still unclear. Some authors argue that cognition in BD is preserved premorbidly and declines after the onset of the illness (Goodwin et al., 2008; Murray et al., 2004). However, other evidence suggests that cognitive deficits might be evident in first-episode BD (Bora and Pantelis, 2015; Lee et al., 2014) and remains largely unchanged thereafter (Bora and Özerdem, 2017a; Samame et al., 2014).

Studies of offspring of patients with BD (BDoff) can aid in dissociating the role of familial predisposition and mood symptoms on cognition. Most studies have investigated the cognitive performance of adult relatives of BD patients (Arts et al., 2008; Balanza-Martinez et al., 2008; Bora and Özerdem, 2017b; Hıdıroğlu et al., 2015; Santos et al., 2017). Some authors suggest that there is no consistent evidence for global cognitive dysfunction in BDoff (Klimes-Dougan et al., 2017;

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Kumar and Frangou, 2010). However, recent years have witnessed increasing number of studies investigating cognitive deficits in offspring and young siblings of patients with BD (de la Serna et al., 2016; Klimes-Dougan et al., 2017; Maziade et al., 2009; Whitney et al., 2013). A recent meta-analysis of the relevant literature (Bora and Özerdem, 2017c) found that compared to controls, youth with positive family history for BD showed dysfunction in verbal and visual memory, attention and processing speed while planning/problem solving and working memory were preserved.

Some authors suggest that premorbid abnormalities in developmental processes may contribute to cognitive dysfunction in youth with familial predisposition to BD independent of current mood symptoms (Bombin et al., 2013; Bora, 2015; Diwadkar et al., 2011; Hanford et al., 2016; McIntyre et al., 2017; Parellada et al., 2017; Surganyes et al., 2017). An alternative explanation is that cognitive dysfunction in these youth might be linked to the history of subclinical mood syndromes particularly since persistent subthreshold manic and depressive symptoms are common among BDoff and might be associated with risk for emergence of BD (Axelson et al., 2015; Mesman et al., 2017). The history of subclinical manic syndromes are particularly essential in definition of Clinical-High-Risk (or Ultra-High-Risk) for BD (Bechdolf et al., 2014; Correll et al., 2014; Van Meter et al., 2016). Attenuated psychotic symptoms also precede BD in some individuals (Correll et al., 2008). The history of depressive symptoms in BDoff (which are also common in the general population) are less predictive in emergence manic symptoms but co-existence of depressive symptoms with subsyndromal manic symptoms, mood lability and attenuated psychotic symptoms might be related to higher risk. In the help-seeking populations, CHR for BD is associated with cognitive difficulties (Metzler et al., 2014) and individuals with attenuated psychotic symptoms who had developed BD at follow-up have also significant cognitive abnormalities (Olvet et al., 2010; Ratheesh et al., 2013). However, a few studies have investigated the potential role of Clinical-High-Risk (CHR) status on cognitive abnormalities in BDoff (Lin et al., 2015). Most notably, Lin and colleagues (Lin et al., 2017) found that visual memory, planning and working memory abnormalities were only evident in BDOff with CHR while only in verbal memory was affected in the offspring without CHR.

In this study, we assessed neurocognitive functioning in 75 BDoff and 50 demographically matched control participants. The BDoff were further categorized into individuals with clinical-high-risk (BDoff + CHR) and those without clinical-high-risk (BDoff-non-CHR). We tested the hypothesis that compared to youth without familial risk to BD, cognitive dysfunction would be present in BDoff irrespective of CHR status, but that the co-existence of familial and clinical high risk would be associated with greater cognitive abnormalities.

2. Experimental procedures

2.1. Participants

The study was conducted at Department of Neuroscience and Department of Psychiatry, Dokuz Eylul University. Offspring aged between 15 and 30 years were identified through patients with BD attending the Bipolar Disorders Outpatient Unit of the Department of Psychiatry. Healthy individuals, aged 15–30 years, without a personal history of psychiatric disorders and without a family history (up to 2nd degree relatives) of mood and psychotic disorders were recruited as controls through advertisements at the university hospital and on the medical school campus. Exclusion criteria for all participants (BDoff and controls) were: (a) personal history of medical disorders; (b) current alcohol/substance abuse; (c) personal history of neurological disorders including head injury; (d) for women, being pregnant or breastfeeding; (e) current use of any medication (e.g., benzodiazepines, stimulants) that could affect neurocognitive testing. For BDoff further exclusion criteria were: personal diagnosis of BD type I, BD type II, schizophrenia spectrum disorders and family history of psychotic disorders. Offspring were designated as having subthreshold syndromes and classified as CHR (BDoff + CHR) if they met one of the following criteria: (a) history of subsyndromal manic symptoms: Experienced two (or more) hypomania symptoms lasting for at least 4 days but not meeting DSM-IV criteria for hypomania (attenuated hypomanic symptoms) OR experienced hypomanic symptoms lasted less than 4 days (brief hypomania); (b) history of depressive episodes along with subsyndromal hypomanic symptoms, mood lability or attenuated psychotic symptoms. No BDoff in this sample had attenuated psychotic symptoms in the absence of depressive or subclinical manic symptoms. The study protocol was approved by the Dokuz Eylul Hospital Ethics Committee for non-interventional studies and all participants provided written informed consent

All assessments were completed by formally trained psychiatry residents who interviewed the participants and their parents (for those below 18 years). The CHR status of BDoff was determined using a modified instrument based on bipolar prodrome symptom scales (Correll et al., 2007; Correll et al., 2014). Depending on their age, all participants were evaluated using either the Schedule for Affective Disorders and Schizophrenia for School-Age Children-lifetime Version (K-SADS-PL) (Kaufman et al., 1997) or the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I) (First et al., 2002). Additionally, BDOff were assessed using the Hamilton Depression Rating Scale (HAM-D-17) (Hamilton, 1960), and the Young Mania Rating Scale (YMRS) (Young et al., 1978). In addition, we calculated the Body Mass Index (BMI) of each individual defined as kg/m^2, where kg was the individual's weight in kilograms and m was their height in meters.

The study sample comprised 75 BDoff (21 BDoff + CHR and 54 BDOff-non-CHR) and 50 demographically matched controls (HC). Details of the sample characteristics are presented in Table 1. Twenty individuals in BDoff-non-CHR group had a history of other nonspecific

Table 1
Comparison of demographic and clinical features between the groups.

	BDoff + CHR (n = 21)	BDoff-non-CHR (n = 54)	HC (n = 50)	p value
Age(mean ± sd)	21.7 ± 4.7	23.0 ± 5.2	23.6 ± 4.6	*,338*
BMI(mean ± sd)	23.6 ± 3.4	23.2 ± 4.5	22.2 ± 3.0	*,300*
Years of education(mean ± sd)	12.6 ± 2.6	13.3 ± 3.1	14.3 ± 2.5	*,039**
Sex				
Female	14 (%66.7)	29 (%53.7)	27 (%54)	*,558*
Current treatment				
no	18 (85,7%)	54 (100,0%)	–	*,026*
yes	3 (14,3%)	0 (0,0%)	–	

HC = healthy control, n = number, sd = Standard deviation,BMI = Body mass index, BD = bipolar disorder, CHR = Clinical-High-Risk,.

Table 2
The comparison of cognitive measures accros groups (corrected for duration of education).

	BDoff + CHR (n = 21)	BDoff-non-CHR (n = 54)	HC (n = 50)	ANOVA		Post-Hoc comparisons			
						BDoff-CHR vs HC	BDoff-non-CHR vs HC	BDoff-CHR vs BDoff-non-CHR	
	Mean ± SD	Mean ± SD	Mean ± SD	F	p	p	p	p	d
Global cognition	**−0.58 ± 0.85**	**−0.23 ± 0.83**	**0.47 ± 0.84**	***13.6***	***<0.001***	***<0.001***	***<0.001***	*0.12*	*−0.40*
Executive function/speed Factor	**0.18 ± 1.00**	**−0.15 ± 0.98**	**0.07 ± 0.99**	0.4	0.52	0.69	0.29	0.22	0.33
-WCSTper	11.3 ± 5.8	11.6 ± 4.5	8.8 ± 4.9	**5.8**	***0.004***	0.14	**0.002**	0.80	0.03
-Trail making B	78.9 ± 29.1	75.5 ± 27.0	64.3 ± 28.1	2.6	0.08	0.06	0.06	0.66	−0.13
-Trail Making A	37.9 ± 17.9	34.8 ± 13.1	27.3 ± 14.3	***5.4***	***0.006***	**0.03**	**0.004**	0.49	−0.21
-WAIS Digit Symbol	61.8 ± 16.5	60.0 ± 12.1	64.7 ± 13.2	*1.9*	*0.15*	0.52	0.05	0.66	0.13
WM-phonologic loop Factor	**0.04 ± 1.00**	**0.11 ± 0.99**	**−0.12 ± 0.99**	0.4	0.66	0.55	0.28	0.81	0.07
-WAIS Digit span backwards	6.4 ± 2.3	7.2 ± 2.1	7.5 ± 2.2	1.7	0.19	0.07	0.51	0.18	−0.37
-WAIS Digit span forwards	7.7 ± 2.2	7.7 ± 2.0	7.7 ± 2.1	0.1	0.99	0.92	0.99	0.99	0
Fluency/central executive Factor	**−0.66 ± 0.88**	**−0.13 ± 0.86**	**0.40 ± 0.87**	***11.0***	***<0.001***	**<0.001**	**0.004**	**0.03**	−0.60
-Letter fluency	36.9 ± 11.9	42.0 ± 11.0	46.6 ± 11.4	***5.0***	***0.008***	**0.003**	0.05	0.10	−0.45
-Semantic fluency	18.9 ± 4.6	21.4 ± 4.3	24.6 ± 4.4	***12.6***	***<0.001***	**<0.001**	**0.001**	**0.03**	−0.56
-ACTT	43.7 ± 6.8	46.7 ± 6.3	52.4 ± 6.6	***14.5***	***<0.001***	**<0.001**	**<0.001**	0.10	−0.40
VisMem Factor	**−0.16 ± 0.97**	**−0.29 ± 0.96**	**0.34 ± 0.97**	**5.0**	***0.008***	**0.05**	**0.002**	0.61	0.13
Visual Reproduction Test Immediate recall	33.6 ± 5.6	33.4 ± 5.2	37.3 ± 5.4	***6.7***	***<0.001***	**0.02**	**0.001**	0.91	0.02
Delay recall	32.6 ± 5.5	32.4 ± 5.2	37.1 ± 5.4	***10.5***	***<0.001***	**0.03**	**<0.001**	0.87	0.02
VerMem Factor	**−0.44 ± 0.99**	**−0.07 ± 0.98**	**0.25 ± 0.99**	**3.3**	**0.04**	**0.01**	0.12	0.17	−0.37
RAVLT learning (Tot1-5)	49.6 ± 7.8	54.1 ± 7.2	58.1 ± 7.5	***8.9***	***0.001***	**<0.001**	**0.01**	**0.03**	−0.60
Long delay recall (list 7)	10.0 ± 2.5	11.2 ± 2.3	12.3 ± 2.4	***7.1***	***0.001***	**<0.001**	**0.02**	0.07	−0.51
Recognition	12.9 ± 1.8	13.3 ± 1.7	14.0 ± 1.7	**3.6**	**0.03**	**0.02**	**0.05**	0.34	−0.23

CHR = Clinical-High-Risk, BDoff = Offsprings of patients with bipolar disorder, HC=Healthy controls.

co-morbid conditions (i.e. anxiety disorder) and others had no history of any mental disorder (eTable-1). Individuals with and without non-specific symptoms within BDOff-non-CHR were coded for subgroup analyses.

2.2. Neuropsychological assessment

Neuropsychological tests were administered to all participants in the same order. Executive functions were measured by Wisconsin Card Sorting Test (WCST) and the Trail Making Test-B (TMT-B) (Heaton, 1981; Reitan, 1958). The outcome variables considered were the number of perseverative errors from the WCST and total time to complete TMT-B. The Rey Verbal Learning Test (RVLT) and Visual Reproduction Test were used to assess verbal (Learning (1–5), delayed recall, recognition) and visual memory (immediate and delayed recall) respectively. The Digit symbol substitution test (DSST) and the Trail Making Test-A (TMT-A) were used as measures of processing speed (Wechsler, 1958; Reitan, 1958). The Digit Span task and the Auditory Consonant Trigrams Test (ACTT) (Stuss et al., 1987) were used to assess working memory. The outcome variables considered were the longest digits backward for the DSB and the total score for the ACTT (3, 9 and 18 s conditions). The phonetic (letters K, A, S) and semantic category tasks indexed verbal fluency (Lezak et al., 2012).

2.3. Data analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21. Chi-square and analysis of variance analysis (ANOVA) were used to compare groups in demographic characteristics. Normality of distribution for all cognitive variables was checked by calculating skewness and kurtosis values. The results showed that, the WCST perseverative errors scores and the time to complete TMT-A and B were not normally distributed. The procedure of two-step normalization transformation to normality in SPSS was used successfully for these variables (Templeton, 2011). Group differences for each neurocognitive test were analyzed with one-way analyses of covariance (ANCOVA) (duration of education as a covariate). A subsequent ANCOVA analysis was conducted by adding the history of co-morbid anxiety disorder as an additional covariate. Effect sizes (Cohen's d) were also calculated for cognitive differences between BDoff + CHR and BDoff-non-CHR.

For calculating composite scores for cognitive domains, we used principle components analysis (PCA) rather than average of z scores of selected tests hypothetically allocated to a cognitive domain as allocation process in the latter procedure might be considered as arbitrary and subjective. PCA, as a dimensionality reduction technique, is also helpful in dealing with multiple comparisons problem. Two types of PCA were conducted: 1) To extract 'global cognition' or “general” factor (g factor). G factor is a single common factor that can be regarded as a summary variable characterizing the correlations between all the different tests in a test battery and typically explains approximately half of the variance. General deficits might explain most of the difference between performances of psychiatric patients and healthy controls (Dickinson et al., 2008). 2) To identify the neurocognitive domains beyond global cognition in healthy controls and BDoff subgroups. In addition to reflecting potential differences in global cognitive factor, group differences in cognitive tests between groups might be related to selective underperformance in some cognitive domains. The optimum number of cognitive components was identified by inspecting the scree plot. Finally, in a supplementary analysis, the effect of impairment in general cognitive factor on between-group differences in cognitive domains and individual cognitive tasks were examined by adding general cognitive factor as an additional covariate in ANCOVA models. This step was conducted to show whether differences between BDoff and healthy controls are fully explainable by a common cognitive factor influencing performance of all cognitive variables.

3. Results

3.1. Demographic and clinical data

As shown in Table 1, the groups were demographically matched except for the duration of education which differed significantly among the groups (p = 0.04) with the HCs having the longest duration of education (Table 2). Three groups were statistically matched for BMI. None of the BDoff-CHR and BDoff-non-CHR participants had current

depressive and hypomanic symptoms (HDRS and YMRS ≤ 8 in all). Only three offspring were on medication (antidepressant and mood stabilizers for depressive or anxiety symptoms) at the time of the study.

3.2. Comparison of neurocognitive factors between the groups

Principal components analysis revealed a global cognition factor that explained 42.0% of variance and a subsequent PCA revealed 5 factor domains including executive functions/processing speed, verbal memory, visual memory, phonological loop (non-executive component of working memory) and fluency/central executive functions. Visual memory immediate and delayed scores were loaded to visual memory domain and all three RAVLT measures (learning, delayed recall and recognition were loaded to the verbal memory domain. TMT-A, TMT-B and WCST were loaded to the executive functions/processing speed domain. Digit span forwards, backwards and ACTT (decreasing loading from digit span forwards to ACTT) were loaded to phonological loop domain. Phonological loop is one of the central concepts of working memory and represents a brief store of verbal information (Baddeley, 1986). Letter and category fluency were the main factors loaded to the fluency/central executive functions domain and only the harder WM variables, but not digit span forward, were modestly loading on this factor. This discrepancy is not surprising as digit span forward is a relatively simple measure of phonological loop and requires minimal contribution of central executive, the other core component of working memory (Baddeley, 1986). On the other hand, digit span backwards and particularly ACTT requires more contribution of central executive compared to digit span forwards. The eTable 2 in the supplement reports correlations between 5 cognitive domains, global cognition factor, individual cognitive variables and years of education.

ANCOVA for global cognition was statistically significant ($F = 13.6$, $p < 0.001$). In post-hoc analyses, both BDoff-non-CHR and BDoff + CHR had significantly lower factor scores on the global cognitive factor compared to healthy controls (Table 3 and Fig. 1). The ANCOVA analyses of specific cognitive factors were significant only in three domains: fluency/central executive factor, visual memory and verbal memory.

Post-hoc analyses showed that both BDoff subgroups significantly underperformed compared to healthy controls in fluency/central executive factor, visual memory and verbal memory (Table 2 and Fig. 1). There were no significant differences in executive function/processing speed, and working memory-phonological loop domains.

In post-hoc analyses, there was no significant difference between BDoff-non-CHR and BDoff + CHR in global cognition and four of five cognitive domains. In one cognitive domain (fluency/central executive factor), BDoff + CHR showed significantly lower performance compared to BDoff-non-CHR ($d = 0.60$, $p = 0.03$).

Adding history of co-morbid anxiety disorders on ANCOVA models had no significant impact on differences between healthy controls and BDoff groups. There were no significant differences between BDoff-non-CHR patients who had history of nonspecific symptoms (i.e. anxiety disorders) and those who were asymptomatic ($p = 0.13$ to 0.66).

3.3. Comparison of performance of individual cognitive tests between the groups

Table 2 provides details of the individual cognitive task performance of BDoff-non-CHR, BDoff + CHR and HC and the statistical group differences. In the ANCOVA analyses, there were significant between-group differences in most individual tests except digit symbol, digit span forwards and backwards (Table 3). In all other tests, group differences were either significant or tended to be significant (Trail making B test, $p = 0.08$) (Table 3).

In post-hoc analyses of significant ANCOVAs, the general pattern emerged was that BDoff subgroups underperformed compared to healthy controls in most individual tests. In post-hoc analyses, group differences between BDOff-non-CHR and BDoff + CHR were not statistically significant (Table 3) for any individual cognitive task except semantic fluency and RAVLT learning. When looking at the effect sizes, BDoff + CHR tended to be associated with more severe deficits compared to BDoff-non-CHR in verbal memory, working memory and verbal fluency tasks (Table 3).

3.4. Global cognition and between-group comparisons of cognitive domains and individual tests

For investigating specific cognitive deficits beyond global cognitive impairment, the ANCOVA analyses for individual cognitive tests were repeated after correcting for global cognition. For individual cognitive tests, after correcting for deficits in global cognition, between-group differences were only significant in the category fluency ($F = 6.4$, $p = 0.002$) and ACTT ($F = 3.9$, $p = 0.02$) tasks.

4. Discussion

The current study investigated neurocognitive function in BDoff-

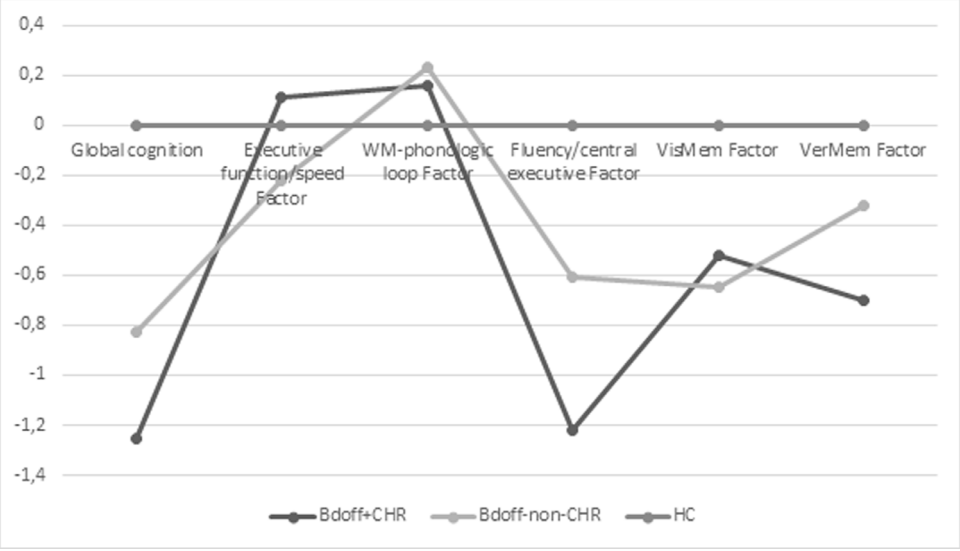

Fig. 1. Z scores of global cognition and cognitive domains in BDoff + CHR and BDoff-non-CHR based on mean and SD of healthy controls.

non-CHR and BDoff-CHR in comparison to healthy individuals without familial predisposition to BD. Cognitive abnormalities were evident in all BDoff irrespective of CHR status. Group differences in individual cognitive tasks were driven by deficits in global cognition and a selective deficit in fluency/central executive domains. There were no significant differences between BDoff + CHR and BDoff-non-CHR in any cognitive measure except in fluency/central executive factor ($p = 0.03$).

4.1. Cognitive dysfunction as an index of familial predisposition

We found that most cognitive deficits were present in BDoff regardless of history of subthreshold bipolar disorder symptoms. These results are in line with those of our recent meta-analysis (Bora and Ozerdem, 2017) which emphasize the role of visual memory and IQ as possible indices of familial predisposition to BD. Furthermore, current findings suggest that underperformance in visual memory tasks in BDoff reflects global cognitive deficits rather than specific deficits in visual learning and recall.

Global cognitive dysfunction in BDoff may be related to abnormal cognitive development in subgroup of patients with BD (Bora, 2015). These deficits might be potentially evident even during childhood (Seidman et al. 2013). Together with other evidence such as increased minor physical anomalies and neurological signs, current findings might support the notion that abnormalities in cognitive development play an important role in BD (Akabaliev et al., 2014; Berecz et al., 2017; Bora, 2015; Bora et al., 2018). However, our results do not unequivocally reveal whether they play a causal or predisposing role to BD onset, or whether they reflect an indirect association with other genetically correlated factors such as socioeconomic status, education level, or comorbid conditions (Abdellaoui et al., 2018).

Current findings suggest that a dysfunction in central executive/fluency domain significantly contributes to neurocognitive profile of BDoff. This factor was related to more complex aspects of working memory, attention, and intrinsic response generation (Supplementary eTable1). This finding suggests that a higher order dysfunction, implicating dysfunction in the central executive component of working memory and supervisory attentional system, as reflected in the ACTT and category fluency task, is associated with familial high-risk for BD (Baddeley, 1986; Shao et al., 2014) whereas dysfunction of the phonological loop or processing speed does not seem related to the risk for BD. Previous studies also supported the notion of an intact phonological loop and dysfunction in the central executive networks in BD (Monks et al., 2004; Thompson et al., 2007). Inefficient connectivity in fronto-parietal control system and cingulo-opercular system might relate to high-order cognitive control (Petersen and Posner, 2012). Emerging evidence suggests that BD might be associated with abnormal connectivity in these networks (Baker et al., 2014; Mamah et al., 2013; Sheffield et al., 2017). Abovementioned findings together with ours may suggest an adverse impact on premorbid academic aptitude which seemingly contradict the work MacCabe et al. (2010) who reported an association between premorbid higher academic achievement and BD. The same study also reported moderately increased risk of bipolar disorder among students with the poorest academic achievement. These inconsistent findings are likely to be related to heterogeneity of BD including some but not all subtypes are associated with premorbid cognitive impairment (Bora, 2015).

4.2. Cognitive dysfunction associated with history of subsyndromal mood disturbance (CHR status)

Current findings suggest that while global cognitive deficits are not specific to BDoff + CHR, there might be cognitive differences in selective high-order cognitive abilities between BDoff + -CHR and BDoff-non-CHR. Emergence of subsyndromal manic or depressive symptoms in BDoff might be potentially related to abnormal development or maladaptive neuroplastic changes in executive control networks. One might also argue that potential loss of acquired cognitive abilities in the context of medical co-morbidities or illness related processes (i.e. toxic effect of symptoms, inflammation) in some BDoff can explain current findings (Balanza-Martinez et al., 2015; Goodwin et al., 2008; McIntyre et al., 2017; Mora et al., 2017; Rosenblat et al., 2015). Alternatively, emergence of subsyndromal symptoms might be a marker of more severe genetic loading for BD among BDoff. Polygenic models, derived from genome-wide data or in linkage studies, are necessary to investigate this possibility. Longitudinal studies investigating cognitive trajectory and subclinical symptoms from childhood to adulthood in BDoff are needed to map the onset of cognitive dysfunction relative to symptom emergence.

The current study adds to available evidence regarding cognitive functioning in individuals with familial risk for BD. More originally, current results provided evidence for shared cognitive dysfunction in all BDoff subgroups but also found selective cognitive differences between BDoff + CHR and BDoff-non-CHR in high-order cognitive tasks. Current findings might have implications for management of individuals with BD in premorbid and prodromal phases of the illness. Cognitive remediation might be effective in BD (Martinez-Aran and Vieta, 2015; Miskowiak et al., 2016) and cognitive rehabilitation in BDoff might be potentially beneficial in improving long-term psychosocial and occupational functioning in individuals at familial risk of BD. Moreover, the cognitive assessment might contribute to the early recognition of BD in premorbid and prodromal phase. Recently, risk calculators, based on clinical and demographic characteristics of BDoff has been proposed (Hafeman et al., 2017). Cognitive dysfunction, together with other potential biomarkers, can help to further develop risk calculators for identifying individuals who are at high risk for BD among BDoff.

The current study has a number of limitations in addition to its cross-sectional design. The relatively small sample size of BDoff + CHR group is a limitation of the study. In addition, cognitive assessment in probands with BD was not available. In addition, no strict correction method for multiple-comparisons (i.e. Bonferroni) was used.

As a conclusion, global cognitive deficits appear to be associated with familial predisposition to BD. The presence of history of subclinical symptoms/CHR status indicated greater severity of impairment in high-order cognitive abilities. The direction of causality cannot be discerned from cross-sectional designs. It is possible that the individuals with greater impairment in high-order cognitive functions are more likely to develop symptoms, or vice versa. Our findings underscore the need for longitudinal studies to map the trajectory of cognitive and clinical symptoms of BD.

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Declaration of Competing Interest

The authors have no conflicts of interest regarding subject of this manuscript.

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Supplementary materials

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